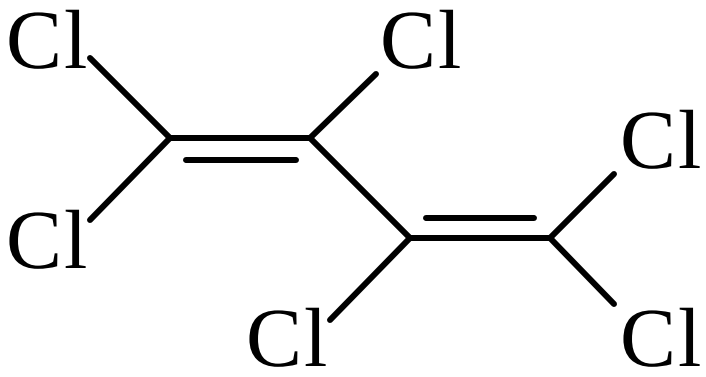
HEXACHLORO-1,3-BUTADIENE (HCBD)



MW 260.76 **CAS No. 87-68-3**

Office of Environmental Health Hazard Assessment

HCBD - OCCURRENCE

- **California** - 4 071 pounds under waste management
- **United States -** 8 000 000 pounds as total production-related waste

BIOTIC LEVELS OF HCBD

- **Fish fat** - 0.01 to 1.2 ppm (near PERC or TCE manufacturing plants)
- **Human adipose tissue** - 1-8 ppb wet weight (Canada)

HCBD - CARCINOGENICITY STUDIES

- No human studies
- Four reports on rodent studies

HCBD - BIOASSAYS (cont'd)

- **Theiss, et al., 1977 - no effect**
  - Mice - Strain A/St, male
  - intraperitoneal injection, three/week, 24 weeks
  - HCBD dissolved in tricaprylin
  - 0, 4, 8 mg/kg
  - evaluated only lungs
  - assay is insensitive to aliphatic chlorides

HCBD - BIOASSAYS (cont'd)

- **Van Duuren, et al., 1979 - no effect**
  - Mice, ICR Swiss, female
  - Dermal application, three/week, 1-1.5 years
  - HCBD (0, 2, 6 mg/mouse) dissolved in acetone
  - no skin tumors
  - lung papillomas ($p<0.05$ by Fisher's Exact Test)

HCBD - BIOASSAYS

- **Chudin, et al., 1985 - no effect**
  - Rats - Wistar, male
  - Daily gavage for two years
  - HCBD dissolved in sunflower oil
  - 0, 0.6, 5.8, 37 mg/kg_{bw}-day

HCBD - BIOASSAYS (cont'd)

- **Kociba, et al., 1977 - two positive bioassays**
  - Kidney tumors
  - Rats, Sprague-Dawley, female / male
  - Diet, two years
  - HCBD dissolved in acetone prior to mixing with feed
  - 0. 0.2, 2.0, 20 mg/kg_{bw}

Kociba et al., 1977a

Tumor Site and Type		Dose (mg HCBD/kg_{bw}-day)			
		0	**0.2**	**2**	**20**
Males					
Renal tubular tumors	Adenoma	1/90	0/40	0/40	3/39 (8%)
	Adenocarcinoma	0/90	0/40	0/40	**7/39 (18%)** **p < 0.001**
	Undifferentiated carcinoma	0/90	0/40	0/40	1/39 (2.6%)
	Renal tubular neoplasms (total)	1/90	0/40	0/40	**9/39 (23%)** **p < 0.0001**
Females					
Renal tubular tumors	Adenoma	0/90	0/40	0/40	**3/40 (8%)** **p = 0.03**
	Adenocarcinoma	0/90	0/40	0/40	2/40 (5%)
	Undifferentiated carcinoma	0/90	0/40	0/40	1/40 (2.5%)
	Renal tubular neoplasms (total)	0/90	0/40	0/40	**6/40 (15%)** **p < 0.001**

HCBD - Initiation/promotion

- **Initiation - no effect** in dermally exposed female mice
- **Promotion - positive** in diet exposed male rats

HCBD - Genotoxicity

- **Bacteria (*Salmonella*)**
  - mutagenicity observed in presence of glutathione / mercapturate /kidney β-lyase pathway
    - GSH, kidney / liver extracts
    - positive with glutathione or cysteine conjugates of HCBD
    - abolished in presence of enzyme inhibitors
  - not mutagenic in presence of CYP-dependent oxidative metabolism

- ***Drosophila***
  - negative for sex-linked recessive lethal mutations

HCBD - Genotoxicity (cont'd)

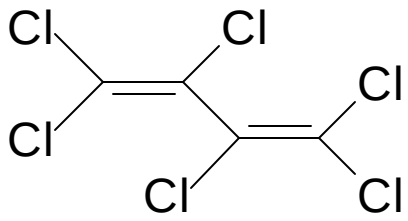
- **Mammalian systems (HCBD and metabolites)**
  - *in vitro* (HCBD and metabolites)
    - **positive** - DNA cross links, UDS, SCE, morphologic transformation
    - **no effect** - CA, SSB
  - *in vivo*
    - **positive** - DNA repair
    - **no effect**- dominant lethal mutations, CA

HCBD-Genotoxicity (cont'd)

- **DNA binding**
  - rat - 0.8 alkylations/10^6 nucleotides in renal DNA
  - mice - covalent binding to renal and hepatic mitochondrial DNA and renal nuclear DNA.

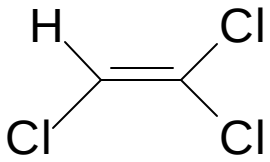
HCBD - Structure Activity

HCBD

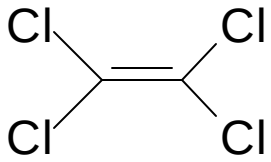


IARC Group 3

Trichloroethylene (TCE)



Tetrachloroethylene (Perc)



IARC Group 2A
Proposition 65

HCBD - Mechanism for Carcinogenicity

- **Genotoxic**
  - bacterial mutagenicity
  - mammalian genotoxicity
  - DNA binding in kidney
- **Non-genotoxic**
  - kidney tumor promotion
  - renal epithelial hyperplasia
  - α_{2u} binding - male rat

HCBD - Summary

- **Carcinogenicity**
  - Renal adenocarcinoma & adenoma and undifferentiated carcinoma in female and male rats fed HCBD for lifetime.
- **Supporting evidence**
  - Mutagenic in bacteria
  - genotoxic in mammalian kidney cells and tissue
  - DNA binding to renal tissue in rats and mice
  - Carcinogenicity of structural analogues
  - Tumor promotion